Determining and Preventing the Potential PERV Problem

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Pig endogenous retroviruses (PERVs) grab headlines because they represent a unique concern for xenotransplantation. Unlike other infectious organisms, DNA copies of PERV make up part of the normal germ line DNA of every cell of their host. Thus, rather than being acquired as an infection, these viral agents are inherited in a Mendelian manner. The germ line nature of PERV renders all barrier technologies ineffective and, as a result, PERV are likely to be the only known microbe that will be introduced into a recipient of pig tissues as the result of a xenotransplant. Indeed, in existing xenotransplant trials using pig tissues, human recipients may have already been exposed to infectious PERV.[1]

In reaction to the realization that an infectious concern due to PERV may exist, and that humans may have already been exposed to PERV, diagnostic tests were rapidly developed and have undergone steady modification and improvement. Using polymerase chain reaction (PCR), researchers now have the ability to detect virus at an exquisite sensitivity and to differentiate between an infection by PERV and merely circulating pig cells (a complication of the monitoring of endogenous retroviruses).[1,2] In addition, sensitive assays have also been developed which detect PERV through the antibody responses raised in an animal against the virus.[3] With the battery of tests now available to researchers, it seems safe to say that, if a PERV infection were to occur, we have the tools to accurately identify and monitor it.

As mentioned above, certain individuals have already been exposed to pig tissues during xenotransplantation trials.[1,4] Retrospective analysis of these patients has facilitated a preliminary insight into the potential for PERV transmission. Reassuringly, these individuals showed no signs of PERV infection. However, although these initial results are encouraging, there remains no room for complacency as the number of individuals tested was small and the exposure to porcine tissues was in most cases extremely transient. Moreover, it is likely that the probability of transmission of PERV will vary significantly depending on the nature of the xenotransplant performed. Factors that are likely to influence PERV transmission include duration of xenograft survival, cell type and number transferred, intimacy of contact between the pig and human cells, immunosuppressive regimen, and perhaps the expression of human complement inhibitors on the donor pig cells.[5,6]

Retrovirologists have been faced with the task of determining the level of risk associated with an agent whose biology currently poses more questions than it supplies answers. In response, comparisons have been made to the virology of closely-related viruses and, with time, valuable new in vitro and in vivo studies will undoubtedly be produced. To date, the biology that has been described suggests that PERV are not likely to represent a significant problem for xenotransplantation. However, it is easy to quote instances where the actual behavior of an organism proved to be that which was initially considered to be the unlikely option. Consequently, further research is clearly required in order to better define the possible significance of PERV on the safety of xenotransplantation.

Future Directions

Although much data have been acquired in vitro regarding PERV infectivity, repeated efforts in several species have failed to produce an in vivo model.

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Recently however, it has been suggested that certain animals may be infectable by PERV.[7] Clearly, the possibility of a representative animal model opens up many avenues of investigation, such as the potential of PERV to cause disease and, perhaps more importantly, information regarding its transmission. Understanding the transmission of PERV is key to determining the microbiological risk associated with this organism. For example, if a recipient of a xenograft were to become infected by PERV, but be incapable of transmitting the virus, then the microbiological risks might well be considered acceptable. If, however, a recipient were to be capable of transmitting the virus to intimate contacts, a possibly unacceptable public health issue would arise.

What might the course of action be in response to a PERV infection in a xenograft recipient? Clearly, if disease were to become apparent, anti-retroviral therapy aimed at decreasing the viral burden would be appropriate. To our advantage, several retrovirus inhibitors already exist which have approval for clinical use. However, because these compounds have been selected for their potency against HIV, it is likely that they will be sub-optimal for treating PERV. Nevertheless, some of these inhibitors show significant activity against PERV, and access to these compounds may prove a useful further level of security in clinical scenarios.[8]

The germ line nature of PERV renders all barrier technologies ineffective and, as a result, PERV are likely to be the only known microbe that will be introduced into a recipient of pig tissues as the result of a xeno-transplant.

PERV-Free Pigs?

Despite all reasonable precautions, the absolute prevention of PERV infection can only be guaranteed by the use of animals that lack these viruses. If pig tissues are used for transplants that contain replication-competent human-tropic PERV, there will be a risk, albeit probably small, of PERV transmission. Unpublished results from several laboratories indicate that pigs carry an unremarkable spectrum of ERV. As expected, the vast majority of PERV loci are replication-defective, with deletions and mutations affecting their ability to encode for virus. As a consequence, although it was originally thought that to obtain pigs devoid of human-tropic PERV was at best a major undertaking, or at worst an impossibility, pigs free of human-tropic PERV may well be an exciting possibility.

Taken together, our knowledge-base regarding PERV suggests that this virus is unlikely to be a major concern for xenotransplantation. Historically, however, society's ability to limit retrovirus transmissions is not impressive, even when armed with the knowledge that a minor change in social behavior could prevent further infections. One might, therefore, predict that prevention should prevail over cure for PERV, an argument that further strengthens the case for searching for pigs devoid of PERV capable of infecting humans.

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